## REMARKS

Claims 86-98 and 100-102 are pending in the application. Claim 90 remains withdrawn.

### 35 U.S.C. § 103

Claims 86-89, 91-98, and 100-102 were rejected under U.S. Pat. No. 6,692,742 ("Nakamura") in view of Lokhorst *et al.*, *Blood* 84:2269-2277, 1994 ("Lokhorst") and Masellis-Smith *et al.*, *Cancer Res.* 57:930-936, 1997 ("Masellis-Smith"). The rejection is respectfully traversed.

Applicants understand the rejection to be based on the following reasoning. The '742 patent is relied on as describing a combination of melphalen and an anti-IL-6 receptor antibody for treatment of multiple myeloma and furthermore that such antibodies reduced the biological activity of IL-6. Lokhorst *et al.* is relied on as teaching that anti-VLA-4 antibodies inhibited binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma and that the antibodies inhibited IL-6 secretion by the LTBMC cells. Masellis-Smith *et al.* is relied on as teaching that anti-alpha4 antibodies that bind alpha4beta7 inhibited multiple myeloma blood B cell interactions with bone marrow fibroblasts *in vitro*. From this the Examiner concluded that it would have been obvious to substitute the anti-IL-6 receptor antibodies taught by the '742 patent with the anti-VLA-4 antibodies taught by Lokhorst *et al.* or Masellis-Smith *et al.* in a method of treating multiple myeloma. The PTO further argued that one of ordinary skill in the art would have been motivated to substitute the anti-IL-6 receptor antibody with the anti-VLA-4 antibody, because antibodies against alpha4 integrin inhibit cell-cell contact which is a prerequisite for IL-6 induction as taught by Lokhorst *et al.* and because antibodies against alpha4 integrin inhibit the adhesion of alpha4beta7 integrin of B cells from multiple myeloma patients with its ligand on the bone marrow (BM) fibroblast and hence prevent extravasation into the BM. Office Action at page 4, first paragraph.

Applicants disagree for the reasons previously described and revisited below and further in view of case law defining current standards of review under 35 U.S.C. § 103. As will be discussed below the argument constructed by the PTO relies on an incorrect reading of the cited art and on misapplication of the law of obviousness.

The biology of IL-6 and its natural ligands, one of which is the membrane bound receptor relied on in the PTO arguments, is far more complex and unpredictable than is allowed for by the PTO arguments.

One need look no further than the '742 reference itself to begin to see the complexity of this field. See, *e.g.*, column 1, of the '742 reference which provides as follows:

> IL-6 is a multifunctional cytokine called B-cell stimulatory factor 2 or interferon .beta.2. IL-6 was discovered as a differentiation factor responsible for activation of B-lymphocytes (Hirano, T. *et al.*, Nature (1986) 324, 73-76). Thereafter, it was found to be a multifunctional cytokine that influences the function of various cells (Akira, S. *et al.*, Adv. in Immunology (1993) 54, 1-78). IL-6 imparts its biological activity through two proteins on the cell membrane.
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> One of them is a ligand-binding protein with a molecular weight of about 80 kD, IL-6 receptor, to which IL-6 binds. IL-6 receptor occurs not only in a membrane-bound form that penetrates and is expressed on the cell membrane but also as a soluble IL-6 receptor consisting mainly of the extracellular region. The other is non-ligand-binding gp130 with a molecular weight of about 130 kD that takes part in signal transmission. IL-6 and IL-6 receptor form a IL-6/IL-6 receptor complex, to which another membrane protein gp130 is bound, and thereby the biological activity of IL-6 is transmitted to the cell (Taga *et al.*, J. Exp. Med. (1987) 166, 967).
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> Emphasis added.

Thus, IL-6, a natural ligand of an IL-6 receptor, is multifunctional and binds to at least two different proteins on the cell surface. In addition, an IL-6 receptor occurs not only on the cell surface but also as a soluble form. These factors alone lead to complexity and unpredictability. For example, one might well expect an antibody to IL-6 receptor to bind the soluble form of the receptor as well as to the membrane bound form. It is not clear from the record if such binding would block binding of endogenous IL-6 to the soluble receptor or what effect that might have on IL-6 mediated cellular processes.

The record is replete with other evidence of the complexity and unpredictability of the field. The Examiner is directed to the Declaration submitted with the Reply to Office Action on September 11, 2006 ("the Mundy Declaration", a copy of which is enclosed). As the Examiner has acknowledged, Applicants presented evidence showing that anti-VLA-4 antibodies and anti-

IL-6 receptor antibodies disrupt very different biological pathways (see the second and third lines of the fifth paragraph of page 4 of the Office Action). For example, Applicants presented evidence that anti-IL-6 receptor antibodies and anti-VLA-4 antibodies will disrupt different biological pathways), a factor which argues strongly against interchangeability of an anti-VLA-4 antibody and an anti-IL-6 receptor antibody. Furthermore, in the Mundy Declaration, Dr. Mundy, an inventor named on the pending application, explained that an anti-IL-6 receptor antibody interacts with at least two different classes of ligands, one class being the gp130 ligands and the other class being the gp80 ligands. An anti-IL-6 receptor antibody will therefore disrupt a multitude of pathways involving these ligands. See the Mundy Declaration at paragraph 7. Dr. Mundy also explained that anti-VLA-4 antibodies are believed to work through mechanisms that are independent of IL-6. See the Mundy Declaration at paragraph 5. Anti-VLA-4 antibodies kill myeloma cells by blocking direct interactions between myeloma cells and normal host cells in the bone marrow. When the myeloma cells cannot attach to the normal host cells, the myeloma cells die. There may be a concomitant decrease in IL-6 levels following administration of anti-VLA-4 (as suggested by the *in vitro* findings of Lokhorst), but this would be a byproduct and not the direct cause of myeloma cell death, nor the reason why the myeloma cells die. This would not lead one of ordinary skill in the art to view an anti-VLA-4 antibody as interchangeable with an anti-IL-6 receptor antibody.

In response to these arguments, the PTO stated that an "obviousness challenge is not limited to the problem the patentee was trying to solve or to only those prior art elements designed to solve the same problem. The combination of 'familiar elements' according to 'known methods' is likely to be obvious when it does no more than yield 'predictable results.'" The Examiner stated that the rationale of combining the references flows logically from (i) the '742 teaching of methods of treating multiple myeloma with anti-IL-6 receptor antibodies and melphalan, where the antibodies inhibit the biological activity of IL-6, to (ii) the Lokhorst *et al.* teaching that monoclonal anti-VLA-4 antibodies inhibit binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma, and where the anti-VLA-4 antibodies inhibited IL-6 secretion. The PTO concluded that given that anti-VLA-4 antibodies inhibit cell-cell contact, and cell-cell contact is a prerequisite for IL-6 induction, one of ordinary skill in the art would be motivated to substitute the anti-IL-6 receptor antibody taught

by the '742 patent with the anti-VLA-4 antibodies taught by Lokhorst *et al.* to yield reduction of IL-6. See page 7 of the present Office Action.

There are several problems with this line of argument, most or all of which are characterized by the PTO's refusal to acknowledge the complexity and unpredictability that permeates this particular field. The use of an anti-VLA-4 antibody to replace an anti-IL-6 receptor antibody is hardly a use of "familiar elements" according to "known methods" to achieve predictable results. The various complexities of these cell signaling pathways (e.g., multiple receptors, membrane bound and soluble receptors, effects on a variety of cells etc.) and the alternate interpretations of the references evidenced in this and previous responses by the Applicants show that this is not a use of "familiar elements" according to "known methods" to achieve predictable results. Applicants presented extensive evidence that one of ordinary skill in the art would interpret the references differently than proposed in the PTO's arguments.

Applicants disagree with the assertion that the prior art teaches the "same methods" to achieve the "same result." The prior art teaches anti-IL-6 receptor antibodies and melphalan for treatment of MM, while Applicants' invention is directed to anti-VLA-4 and melphalan combination to treat MM.

Applicants disagree with Examiner's statement that one of ordinary skill in the art would be motivated to substitute the anti-IL-6 receptor antibody taught by the '742 patent with the anti-VLA-4 antibodies taught by Lokhorst *et al.* to yield reduction of IL-6. One of ordinary skill in the art would read Lokhorst *et al.* to teach that it is the disruption of the cell-cell interaction that leads to death of the multiple myeloma cells, and would interpret the observation of decreased IL-6 levels as a by-product of the effect. By contrast, one of skill in the art would read the '742 patent to teach that the decreased biological activity of IL-6 was essential to the observed effect on myeloma cells. There is no indication in the '742 patent that anti-IL-6 receptor antibodies inhibit cell-cell contact.

The PTO must read the references in context as one of ordinary skill in the art would read the references at the time the invention was made. MPEP 2141.01(III). The PTO has not done this. Instead, the PTO has pulled two similar observations from the '742 patent and the Lokhorst *et al.* patent and ignored the context of the references. Without the benefit of hindsight, one of

ordinary skill in the art would not have linked the observed decrease in IL-6 function reported in the '742 patent, with the decrease in IL-6 secretion taught by Lokhorst *et al.*

The Examiner responded by arguing that the mechanism of action does not have a bearing on the patentability of the invention, if the invention was already known or obvious, and concluded that Applicants' proposed mechanism of action for the anti-VLA-4 antibody and melphalan combination therapy for treatment of multiple myeloma does not distinguish the prior art teaching the same methods to achieve the same end result.

There are several problems with this argument. First, it puts the cart before the horse. The argument assumes the invention is not patentably distinct and then goes on to discuss how a mechanistic insight can't make the invention patentable. Second, while Applicants express no view on whether the PTO position on mechanism and patentability is correct, Applicants point out that the PTO position is irrelevant to the instant matter. The Applicants are not arguing that there are different mechanisms and that that should make claims to something disclosed in the art patentable. The argument is that the Examiner improperly interprets references such as Lokhorst *et al.* to teach one "mechanism" which he then relies on in the obviousness argument to support interchangeability of an anti-VLA-4 antibody and an anti-IL-6 antibody. The Applicants have provided evidence that one of ordinary skill in the art would have come away from Lokhorst *et al.* with a different view of the "mechanism" disclosed by the reference, one that argues against interchangeability of an anti-VLA-4 antibody and an anti-IL-6 antibody. According to the evidence presented by the Applicants, one of ordinary skill in the art would not believe the experiments in Lokhorst *et al.* were acting through a VLA-4 mediated pathway. Therefore, based on the understanding of the mechanism at work in the experiments in the reference, one of ordinary skill in the art would not interpret the references in the same way as the PTO. For example, one of ordinary skill in the art would not believe the experiments in Lokhorst *et al.* to be working in a way that would make it obvious to substitute a VLA-4 antibody for an anti-IL-6 receptor antibody. The Examiner assumes that the invention was known or obvious, and that the only difference is a difference in the appreciation of mechanism. The situation here is quite different. The instant matter presents a situation where one of ordinary skill would not believe the art to be operating by the mechanism proposed by the PTO but by a different mechanism. Proper understanding of the Lokhorst *et al.* reference deprives the PTO argument of at least one

critical element. When one views the art as teaching different mechanisms, the references do not render the claims obvious.

Other evidence provided by the Applicants further shows the unpredictability and confusion in the field and the art. The Mundy Declaration noted that the prior art reference Bataille *et al.* (*Blood* 86:685-691, 1995; cited in the IDS submitted June 21, 2002) taught that anti-IL-6 antibodies were not effective at treating multiple myeloma. Bataille *et al.* reported that patients with advanced multiple myeloma did not achieve remission or improved outcome following treatment with murine anti-IL-6 monoclonal antibodies. See the Mundy Declaration at paragraph 4. The '472 patent also disclosed that IL-6 receptor antibodies alone were ineffective in the absence of chemotherapeutic agent. See the '472 patent at col. 20, lines 23-35; and col. 22, lines 13-20 and 49-53, and Table 2. Thus, even if anti-VLA-4 antibodies inhibit IL-6 (which Examiner reads Lokhorst to suggest), one would not expect IL-6 inhibitory agents to be interchangeable with anti-VLA-4 inhibitory agents to effectively treat multiple myeloma, whether alone or in combination with any other agent.

The PTO responded to this position by stating that Examiner's position was that both the '742 patent and the claimed invention are directed to combination therapy in treating multiple myeloma. Again this assumes the answer the PTO wants. Both the art and the claims are directed to combinations of an antibody with another agent but the antibodies are different, anti-IL-6 in the case of the art and anti-VLA-4 in the case of the claims. The central issue here is whether the antibodies against very different targets are interchangeable. The fact that at least some references show that anti-IL-6 antibodies do not work undercuts and weakens any suggestion that they would work the same alone or in a combination. The issue also goes to complexity and unpredictability which is ignored in the PTO analysis. At the filing date of the application, one of ordinary skill in the art would understand that Bataille *et al.* teaches that anti-IL-6 receptor antibodies alone are not effective for treatment of multiple myeloma. In addition, the PTO seems to imply that Bataille *et al.* teaches a treatment of multiple myeloma by the statement: "the claims are directed to methods of treatment, not methods of curing. Accordingly, any measurable level of improvement in either Bataille *et al.* or the '742 patent is considered a treatment of multiple myeloma." See the Office Action at the paragraph spanning pages 5-6.

This is an incorrect reading of the reference. The effect reported in Bataille *et al.* was not significant. The PTO cannot read an insignificant result as any type of improvement. It is well-known in any scientific field that a non-significant result is within the expected range of error and therefore cannot be accorded any weight whatsoever.

The PTO also discussed Applicants' surprising synergistic results, which were presented in the May 16th Reply, which is incorporated and relied on here with the entire file history. These results indicated a significant decrease in serum IgG2 levels (an indicator of decreased tumor burden) in mice treated with a combination of anti-VLA-4 antibodies and melphalan, whereas no significant decrease was observed following treatment with either agent alone in this particular experimental model.

The PTO responded to Applicants' surprising results by asserting that the same surprising "synergistic results" were taught by the '742 patent. Office Action at page 6. The PTO defended this position by pointing out that the '742 patent teaches that the combination of a nitrogen mustard anticancer agent (such as melphalan) and anti-IL-6 receptor antibodies had a synergistic effect for treatment of MM. Again this assumes the answer the PTO wants. Both the art and the claims are directed to combinations of an antibody with another agent but the antibodies are different, anti-IL-6 in the case of the art, and anti-VLA-4 in the case of the claims. The central issue here is whether the antibodies against very different targets are interchangeable. The allegedly synergistic results taught by the '742 patent are not the same as Applicants' synergistic results, at least because one of ordinary skill in the art at the priority filing date of the application would not have read the combination teachings of the prior art to suggest that the anti-VLA4 antibodies of Lokhorst *et al.* could be substituted for the anti-IL-6 receptor antibodies of the '742 patent.

Applicants stated in the October 31st reply that there is no explicit or implicit suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art to modify the teachings of the '742 patent, Masellis-Smith *et al.*, and Lokhorst *et al.* to arrive at the claimed methods.

The Examiner responded by stating that "the rationale to support a conclusion that the claims would have been obvious is that all claimed elements are known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods with no

change in their respective functions and the combination would have yielded nothing more than predictable results of treating MM. The Examiner's position is that the combined reference teachings provide teachings, suggestion and motivation to treat MM with anti-VLA-4 antibodies and chemotherapeutic agent." Office Action at page 7, emphasis added. By "claimed elements," Applicants assume the Examiner means at least (i) a combination of (ii) anti-VLA4 antibodies and (iii) a chemotherapeutic agent for (iv) treatment of multiple myeloma.

Anti-VLA-4 antibodies and treatment of multiple myeloma are disclosed in Lokhorst *et al.*, and a chemotherapeutic agent/anti-IL-6 antibody combination therapy for treatment of multiple myeloma are disclosed in the '742 patent. However, there is no suggestion or motivation to combine these teachings to arrive at the claimed invention, because one of ordinary skill in the art would not be motivated to substitute the anti-IL-6 receptor antibodies of the '742 patent with the anti-VLA-4 antibodies of Lokhorst *et al.*, even though Lokhorst *et al.* showed decreased IL-6 secretion in the presence of anti-VLA-4 antibody and the '742 patent taught decreased IL-6 function in the presence of anti-IL-6 receptor antibodies.

The PTO stated that "the reason to substitute is to decrease the production of IL-6 (directly or indirectly) mediated by the cell surface VLA-4 ligation, wherein the IL-6 enhances MM cell growth and proliferation…Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not." Office Action at page 7. Applicants maintain however that one of ordinary skill in the art at the filing date of the application would have viewed the observations of Lokhorst *et al.* with respect to the decreased IL-6 secretion as a byproduct of the decreased cell-cell interaction, and would view the decreased cell-cell interaction as the key to multiple myeloma cell death. There is nothing in the '742 patent to indicate that the anti-IL-6 receptor antibody caused a decrease in cell-cell interactions. The PTO is asking one of ordinary skill in the art at the priority filing date of the application to make an impossibly large leap to view the teachings of the '742 patent and Lokhorst *et al.*, and to arrive at the claimed combination therapy. The steps that led to the observed effects in the '742 patent and Lokhorst *et al.* were too different, and one of ordinary skill would not have linked the two. It is only by impermissible hindsight that the PTO is able to make the required leap.

In the October 31st reply, Applicants stated that in view of the evidence as a whole, one of ordinary skill in the art would not have found a reason in the '742 patent to substitute the anti-IL-6 receptor antibodies of the '742 patent with the anti-VLA-4 antibodies in combination with a chemotherapeutic agent for treatment of multiple myeloma, even in view of one or both of Lokhorst *et al.* and Masellis-Smith *et al.*

The PTO appears to have the view that Applicants' point is not persuasive because it is directed to effects observed with the use of anti-IL-6 receptor antibodies alone. The PTO maintains that because the claims are directed to a combination therapy, and (i) the '742 patent teaches a combination therapy of anti-IL-6 receptor antibody in combination with a chemotherapeutic agent in treatment of multiple myeloma, and (ii) Lokhorst *et al.* teaches that anti-VLA-4 antibodies inhibited binding of purified myeloma cells to LTBMC cells *in vitro* and inhibition of this cell-cell contact inhibited IL-6 secretion by the LTBMC cells, the skilled in the art at the time of Applicants' invention would have been motivated to substitute the anti-IL-6 receptor antibody with the anti-VLA-4 antibody in combination with a chemotherapeutic agent for treatment of multiple myeloma. As stated repeatedly above, the PTO is making too great a leap, and one of skill in the art would not have been motivated to substitute the anti-IL-6 receptor antibody with the anti-VLA-4 antibody in combination with a chemotherapeutic agent for treatment of MM.

The PTO arguments quoted KSR as stating "The combination of familiar elements according to known methods is likely to be obvious when it does not more than yield predictable results." The PTO's reliance on KSR is misplaced. The PTO's argument takes obviousness analysis well outside the bounds of the case law and, in particular, far beyond the limits set in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007).

The facts in *KSR* involved a small number of simple elements, combined in a straight-forward way, in the context of a highly predictable technology. The decision in *KSR* criticized the court below for rigid application of the teaching, suggestion, or motivation test (the TSM test) and for reliance on the proposition "that a patent claim cannot be proved obvious by merely showing that the combination of elements was "obvious to try." The Supreme Court allowed

that, under certain carefully delineated circumstances, "obvious to try" might be an acceptable test, and indeed found it an acceptable test for the fact pattern before it. The *KSR* Court was very careful, however, to qualify its language and limit its holding to distinguish the simple predictable fact pattern based on a the combination of a few identified, known simple elements in a predictable art to meet a known problem found in *KSR* from more complex and unpredictable fact patterns, such as the one in the instant matter. The language of the holding in *KSR* is instructive:

> The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try " When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.

*KSR* at 1742 (emphasis added, citations omitted).

The facts in the instant matter do not present a finite number of identified, predictable solutions. Evidence presented by the Applicants show the field was complex and that the effects of the relevant antibodies were unpredictable. The art cannot be properly interpreted to say that an anti-IL-6 antibody can predictably replace an anti-VLA-4 antibody. As evidenced by this and previous submissions, the pathways are too complex, the receptors and ligands involved affect too many different cells and pathways, and the references are open to too many interpretations to allow one to say that an anti-IL-6 antibody can predictably replace an anti-VLA-4 antibody. The fact pattern of the instant matter bears no resemblance to the fact patterns characterized by "a finite number of identified, predictable solutions," and found by the *KSR* Court to be appropriate for "obvious to try analysis." In short, the claims are unobvious under *KSR*.

*KSR* was careful to limit the analytical framework for determining obvious in unpredictable areas. In a recent case, *Eisai Co. Ltd. And Eisai, Inc., v. Dr. Reddy's Laboratories Ltd and Dr. Reddy's Laboratories, Inc., and Teva pharmaceuticals USA Inc.*, 2007-1397, -1398, (Fed. Cir. 2008) the Federal Circuit applied the holding of KSR. The Federal Circuit expressly acknowledged the sharp limitations the Supreme Court placed on the analysis when applied in

the unpredictable arts. The holding in *Eisai* compels a finding of non-obviousness in the instant matter. The *Eisai* court provided the following analytical framework:

> The Supreme Court's analysis in *KSR* thus relies on several assumptions about the prior art landscape. First, *KSR* assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, *KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. *See Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound."). Third, the Supreme Court's analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S. Ct. at 1742. In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, *KSR's* focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.
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> Emphasis added.

This analysis requires at least three elements. Even if the art provided the first required element, a starting point, namely the use of an anti-IL-6 receptor antibody, it fails utterly to provide the second element. Application of *KSR*, as interpreted in *Eisai*, includes the following element, "Second, *KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound." That element is entirely lacking—as discussed above the art provides no reason to believe an anti-VLA-4 antibody could be used in the place of an anti-IL-6 receptor antibodies. There is reason to make a particular modification to achieve the claimed compound. The art also fails to provide the third element. The art does not supply the required assembly of a "finite number of identified, predictable solutions."

Clearly, the "solutions" provided by the art fall short of being "genuinely predictable" as mandated in *Eisai*. The PTO arguments fail to pass the "difficult hurdle" recognized by the *Eisai* court and presented by the complex and unpredictable technology at issue here.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 USC § 103.

## CONCLUSION

In view of the foregoing, Applicants contend that the present claims are in condition for allowance, and notice to this effect is respectfully requested. Should the Examiner maintain any of the present grounds for rejection, the favor of a telephone call to the undersigned is respectfully requested.

A Petition for Extension of Time for three months is attached. Please apply the fee of $1050 for the Petition, and any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. B2047-700731.

Respectfully submitted,

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